PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference BP/G-33581A/LEK	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/SI2004/000043	International filing date *(day/month/year)* 22.12.2004	Priority date *(day/month/year)* 23.12.2003
International Patent Classification (IPC) or national classification and IPC A61K38/19, A61K47/20		
Applicant LEK PHARMACEUTICALS D.D. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.10.2005	18.11.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Schifferer, H Telephone No. +49 89 2399-

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SI2004/000043

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-18 as originally filed

Claims, Numbers

1-16 as originally filed

Drawings, Sheets

1/2-2/2 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3, 4, 6-9, 11
	No:	Claims	1,2,5,10,12-16
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	3, 4, 6-9, 11
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	-

2. Citations and explanations (Rule 70.7):

see separate sheet

V Reasoned statement under Rule 66.2 (a) (ii) with regard to novelty, inventive step or industrial applicability

1) Clarity

1.1) In claim 1 formula 1 refers to the remains R1, R2, R3. Additionally claim 1 explains R4 being $(CH_2)_n$, wherein n is between 1 and 6. This R4 cannot be found in the formula 1. The same applies to the present description on page 4, second paragraph. This discrepancy between the formula and the corresponding reference in claim 1/present description causes a lack of clarity and thus leaves the exact meaning and scope of protection unclear (Article 6 PCT).

1.2) The term "non-detergent sulphobetaine" - in particular the property of being "non-detergent" - cannot be considered clear and precise, since this is not a common scientific, well-known substance class. Thus an objection of clarity is raised for the subject-matter of claims 1 /(2-16 in part) according to Article 6 PCT.

1.3) Claim 13 is construed as if it was a second medical use claim. However, the complaints or diseases are missing, the treatment or prevention of which should be anticipated. This results in a lack of clarity in the sense of Article 6 PCT.

2) Documents

The following documents (D1-D3) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: US 5 500 416 A (MIYAZAWA ET AL) 19 March 1996 (1996-03-19)
D2: WO 97/25404 A (THE PROCTER &; GAMBLE COMPANY; ROMANO, NICOLETTA; TRANI, MARINA; MINERV) 17 July 1997 (1997-07-17)
D3: WO 99/52550 A (ASTRA AKTIEBOLAG; CARLSSON, HANS; LARSSON, ANETTE; SOEDERLIND, ERIK) 21 October 1999 (1999-10-21)

Unless otherwise specified, reference is made to the respective cited passages in D1-D3 (see the International Search Report, Form PCT/ISA/210).

3) Novelty - Article 33 (1) and (2) PCT

3.1) D1 discloses a dermatological preparation containing a dermatological base, a drug (organic molecules) and a percutaneous absorption promoting agent which in itself comprises a) at least one anionic surfactant and b) at least one surfactant having a nitrogen atom in the molecule other than anionic and cationic surfactants where sulphobetaine is proposed. Sulphobetaine is explicitly used as percutaneous absorption promoting agent.
With D2 a disinfecting composition is described which comprises hydrogen peroxide, an antimicrobial essential oil, a surfactant, such as betaine or sulphobetaine, buffers and stabilizers.

A vaccine delivery system for SC administration is disclosed with D3, which is based on a protein antigen, polymer particles/polymer matrix, buffers and sulphobetaine.

3.2) In the light of D1 -D3 (see sections V-2, 3.1) and under consideration of sections V-1.1-1.3, the subject-matter of claims 1,2,5,10,12-16 is considered not novel according to Article 33 (1) and (2) PCT. The "use" claims 14-16 are regarded as focussing on a known product which is in a form in which it is in fact also suitable for the stated use. Though never been described for that use, documents D1-D3 deprive the subject-matter of claims 14-16 of novelty (PCT International Search and Preliminary Examination Guidelines. March 25th, 2004. Page 41, Chapter 5.21).

3.3) Consequently, - under consideration of V-1.1-1.3 - the subject-matter of claims 3, 4, 6-9, 11 appears to be novel (Article 33 (1), (2) PCT), since its corresponding content is not disclosed by D1-D3.

4) Inventive Step - Article 33 (1) and (3) PCT

4.1) The problem posed in the present application was the development of stabilised pharmaceutical compositions, in particular such based on proteins.

The solution according to the Applicant was a pharmaceutical excipient comprising the active principle and sulphobetaine.

D3 which is regarded closest prior art discloses a vaccine delivery system for SC administration, which is based on a protein antigen, polymer particles/polymer matrix and sulphobetaine.

D3 does not disclose the use of granulocyte-colony stimulating factor, of those agents listed in claim 3, and those sulphobetaine derivatives given in claim 6. D3 does not use sulphobetaine as buffer, pH adjusting agent.

It appears to be obvious to a person skilled in the art to derive the use of sulphobetaine derivatives or other protein structures and organic macromolecules for a sulphobetaine containing formulation of an improved pharmaceutical stability.

Unexpected or surprising effects do not seem to be connected with the use of further sulphobetaine derivatives and other proteins. There is no evidence in current application that sulphobetaine might work as buffer or pH adjusting agent.

4.2) Therefore, under provision of V-1.1-1.3, the subject-matter of claims 3, 4, 6-9, 11 is obvious to a person skilled in the art due to general textbook knowledge. Thus the aforementioned subject-matter does not meet the requirements of Article 33 (1) and (3) PCT in that extent that it cannot be considered inventive.

5) Further remarks

The Applicant's attention is drawn to the fact that the application must not be altered thus that its

subject-matter might exceed the contents of the application originally filed (Article 41 (2) PCT).